DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022200

NDA APPROVAL

Amylin Pharmaceuticals, Inc.
Orville Kolterman, M.D.
Sr. Vice President, Research & Development
9360 Towne Centre Drive, Suite 110
San Diego, CA 92121

Dear Dr. Kolterman:

Please refer to your new drug application (NDA) submitted on May 4, 2009 and received May 5, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for BYDUREON (exenatide extended-release for injectable suspension).

We acknowledge receipt of your amendments dated July 28, August 15, 16, 25, September 22, October 4, 20, 24, November 3, and December 8, 2011, and January 10 and 24, 2012.

The July 28, 2011, submission constituted a complete response to our October 18, 2010, action letter.

This new drug application provides for the use of BYDUREON (exenatide extended-release for injectable suspension) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in multiple clinical settings.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your January 24, 2012, submission containing final printed carton and container labels.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 9 years (inclusive) because the necessary studies are impossible or highly impractical. This is because there are too few children in this age range with type 2 diabetes mellitus to study.

We are deferring submission of your pediatric studies for ages 10 to 17 years (inclusive) until July 2017, because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

1860-1 A randomized and controlled pediatric study under PREA to evaluate the safety, efficacy, and pharmacokinetics of BYDUREON (exenatide extended-release for injectable suspension) for the treatment of type 2 diabetes mellitus in pediatric patients ages 10-17 years (inclusive).

The timetable you submitted on December 18, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/2012
Study Completion:	01/2017
Final Report Submission:	07/2017

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of medullary thyroid carcinoma or a signal of a serious risk of adverse cardiovascular events.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1860-2 A 2-year study in mice to determine the reversibility of C-cell hyperplasia, the potential of hyperplasia to progress to neoplasia, and GLP-1 receptor expression on C-cells after 6 months of treatment with exenatide for injectable suspension.

The timetable you submitted on December 18, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2012
Study Completion:	05/2015
Final Report Submission:	03/2016

1860-3 A study to evaluate and compare GLP-1 receptor expression/density on human, rat, and mouse thyroid C-cells. This should include evaluation of mouse tissue from PMR 1860-2 following exenatide for injectable suspension treatment for 6 months as well as following 1.5 year recovery.

The timetable you submitted on December 18, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	10/2012
Study Completion:	05/2015
Final Report Submission:	11/2015

1860-4 A study to evaluate the dependence of the GLP-1 receptor for exenatide-induced C-cell hyperplasia and investigate the expression of growth regulatory genes in wild-type and GLP-1 receptor knock-out mice.

The timetable you submitted on December 18, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2012
Study Completion:	06/2013
Final Report Submission:	12/2013

1860-5 A medullary thyroid carcinoma case series registry of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in

the United States and to identify any increase related to the introduction of BYDUREON (exenatide for injectable suspension) into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to diabetes and use of BYDUREON (exenatide for injectable suspension).

The timetable you submitted on December 18, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	07/2012
Study Completion:	09/2027
Final Report Submission:	09/2028

Finally, there have been signals of a serious risk of cardiovascular events with some medications developed for the treatment of type 2 diabetes mellitus, and available data have not definitively excluded the potential for this serious risk with BYDUREON (exenatide extended-release for injectable suspension). We have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of cardiovascular events with antidiabetic medications, including BYDUREON (exenatide extended-release for injectable suspension). Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1860-6 A randomized, double blind, placebo-controlled trial evaluating the effect of BYDUREON (exenatide extended-release for injectable suspension) on the incidence of major adverse cardiovascular events (MACE) in subjects with type 2 diabetes mellitus (T2DM). The trial must also assess adverse events of interest including the long-term effects of BYDUREON (exenatide extended-release for injectable suspension) on potential biomarkers of medullary thyroid carcinoma (e.g., serum calcitonin) as well as long-term effects on thyroid neoplasms, pancreatitis (including hemorrhagic and necrotizing forms), pancreatic cancer, serious injection site reactions (including nodules), allergic/hypersensitivity events, serious hypoglycemia, and renal disorders.

The timetable you submitted on December 18, 2011, states that you will conduct this trial according to the following schedule:

Trial Completion:	07/2018
Final Report Submission:	12/2018

Submit the protocols to your IND 067092, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. The details of the REMS requirements were outlined in our REMS notification letter dated February 16, 2010.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for BYDUREON (exenatide extended-release for injectable suspension) to ensure the benefits of the drug outweigh the risks of medullary thyroid carcinoma and acute pancreatitis, including hemorrhagic and necrotizing pancreatitis.

Although we continue to believe that a REMS is necessary to ensure that the benefits of BYDUREON (exenatide extended-release for injectable suspension) outweigh its risks, upon further consideration, we have determined that a Medication Guide is not necessary as part of the REMS to ensure the benefits of the drug outweigh the risks described above because maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208.1. Therefore, it is no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of BYDUREON (exenatide extended-release for injectable suspension) outweigh its risks.

Your proposed REMS, submitted on January 24, 2012, and appended to this letter, is approved. The REMS consists of a communication plan and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce BYDUREON (exenatide extended-release for injectable suspension) into interstate commerce.

The REMS assessment plan should include, but is not limited to, the following:

1. The 1-year, 2-year, and 7th-year REMS assessment reports will include the following:

    a) The results of surveys assessing healthcare providers' understanding of the critical content related to pancreatitis and medullary thyroid cancer. The assessment will include healthcare providers' awareness of appropriate BYDUREON (exenatide extended-release for injectable suspension) patient population characteristics, the potential risk for medullary thyroid carcinoma, and the need for prompt evaluation of patients who develop symptoms suggestive of pancreatitis.

    b) The results of surveys assessing healthcare providers' identification and treatment of medullary thyroid carcinoma and acute pancreatitis after initiation of BYDUREON (exenatide extended-release for injectable suspension).

    c) The results of case series review of targeted safety surveillance of spontaneously reported cases of acute pancreatitis.

    d) The percentage of targeted prescribers who are presented with the Highlighted Information for Prescribers via sales specialists or medical information department.

    e) An analysis of use data establishing the extent of first-line use of BYDUREON (exenatide extended-release for injectable suspension).

    f) An evaluation of the extent to which the elements of the REMS are meeting the goals of the REMS and whether modifications to the elements or goals are needed.

2. The 1-year REMS assessment report will include the number of letters sent via email, standard mail, and facsimile, and the dates the letters were sent. For the letters sent via email, include the number of letters sent via standard mail because the healthcare provider did not have an email address, and the number sent because the email was undeliverable. For letters sent via email, include the number of letters successfully delivered, and the number of email letters opened by the recipients.

3. Information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

You should update the REMS supporting document to include the following:

- a detailed document outlining the final methodology and content of the healthcare provider survey at least 90 days prior to initiating the conduct of the survey. Three healthcare provider surveys will be conducted in accordance with the timeline for submission of assessments of the REMS: 1 year, 2 years, and in the 7th year.

- a detailed document outlining the final methodology for conducting case review evaluations of pancreatitis at least 90 days prior to initiating the evaluation. Three evaluations will be conducted in accordance with the timeline for submission of assessments of the REMS: 1 year, 2 years, and in the 7th year.

- any additional instruments and methodology for your REMS assessments that are not included in the REMS supporting document.

Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022200 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022200 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 022200
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 022200
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

We request that for a period of two years, you submit all cases of hemorrhagic and/or necrotizing pancreatitis and all cases of suspected or confirmed reports of acute pancreatitis with an outcome of death as 15-day alert reports, and that you provide analyses of clinical trial and post-marketing reports of pancreatitis, including hemorrhagic and/or necrotizing pancreatitis, as adverse events of special interest in your periodic safety update reports.

If you have any questions, please call Pooja Dharia, Pharm.D., Regulatory Project Manager, at (301) 796-5332.

Sincerely,

{See appended electronic signature page}

Mary Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
- Package Insert
- Medication Guide
- Instructions for Use
- Carton and Container Labeling
- REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY H PARKS
01/27/2012